

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of

MASSFELDER et al.

Atty. Ref.: 3665-133; Confirmation No. 9193

Appl. No. 10/520,085

TC/A.U. 1643

Filed: January 5, 2005

Examiner: Gussow

For: USE OF PTHRP ANTAGONISTS FOR TREATING RENAL CELL CARCINOMA

\* \* \* \* \*

February 14, 2008

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**SUPPLEMENTAL SUBMISSION**

Supplemental to the RCE and Amendment filed January 10, 2008, attached is a Rule 132 Declaration of Thierry MASSFELDER in support of the claimed invention.

An early and favorable Action is requested.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

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**MASSFELDER et al.**Atty. Ref.: **3665-133**Serial No. **10/520,085**Group: **1643**Filed: **January 5, 2005**Examiner: **Gussow**For: **USE OF PTHRP ANTAGONISTS FOR TREATING RENAL  
CELL CARCINOMA**

\* \* \* \* \*

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

**RULE 132 DECLARATION**

I, Thierry MASSFELDER, do hereby declare and say as follows:

1. I am aware of the above-identified application, and am fully informed of the invention claimed therein. I am inventor of the subject matter claimed in the above.

3. I am currently a Researcher (tenure) in INSERM (French Institute of Health and Medical Research), Team leader "search of new therapeutic and pronostic options for human kidney cancer", Renal Pharmacology and Physiopathology Laboratory INSERM Unit 727, Université Louis Pasteur, 11, rue Humann, Bât 4, 1er étage, 67085 Strasbourg Cedex. I hold an Extensive Research Degree ("D.E.A" in French) in Pharmacology and Pharmacochimistry, Molecular and Cellular Pharmacology option, from Louis Pasteur University (ULP), Strasbourg, FRANCE, earned in 1991; obtained with distinction (mention "bien"), allowing entry into the rankings for financial support by the French Government (Allocation de Recherche du MENRT). I further hold a PhD in Molecular and Cellular Pharmacology, ULP, Strasbourg, FRANCE, earned in 1994;

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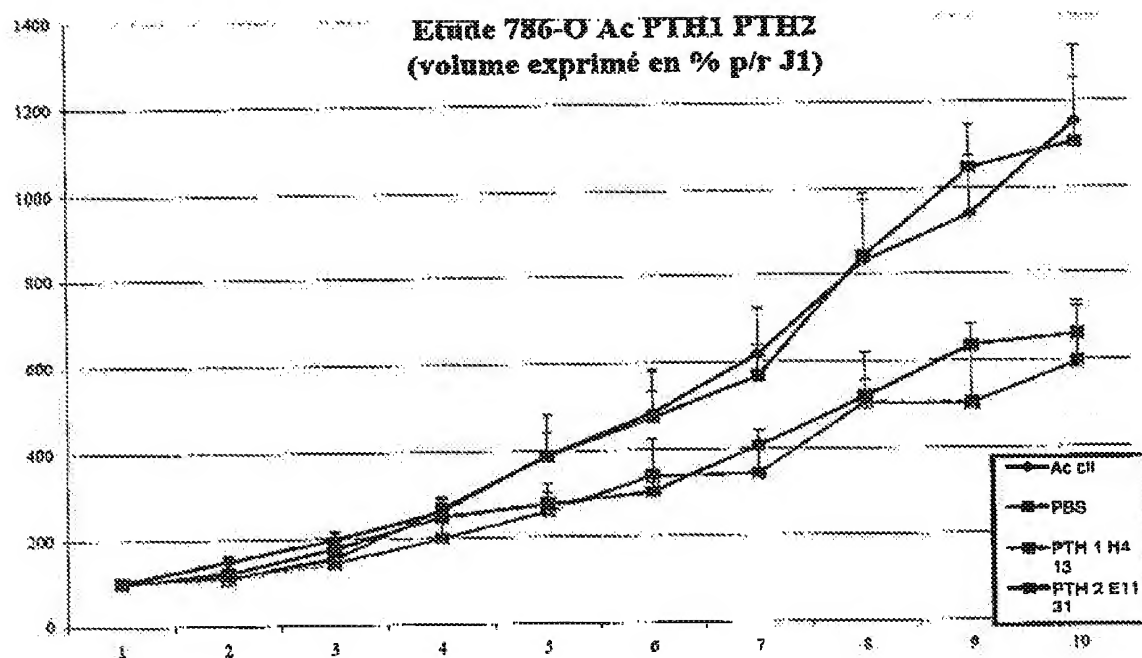
**Rule 132 DECLARATION**

obtained with the highest possible distinction (mention "très honorable avec félicitations"), sparingly attributed by the ULP of Strasbourg. I earned a University Diploma: "Scientific manager in animal experimentation", in 2001, ULP (mention "assez bien").

4. I believe the above-identified application demonstrates, such as in Figures 4, 6 and 8, that an anti-PTHrP antibody directed against the intermediate or C-terminal regions of PTHrP, in particular anti-PTHrP (34-53) antibody and anti-PTHrP (107-139) antibody, decrease the proliferation of tumor cells.

5. To further demonstrate this effect I have produced, or had produced under my direction and control, two further distinct monoclonal anti-PTHrP (34-53) antibodies, called PTH1 H413 and PTH2 E1131 which demonstrated the important in vivo anti-tumoral effect of these antibodies. The following figure is a graph showing the percentage of tumoral volume in comparison with the volume of day 1 (day 1 is 100%) for two controls (PBS or non relevant antibody (AC ctl) of the same antibody isotype than PTH1 and2 and directed against Stra8, a protein expressed in male gonades and testis) (two upper curves) and the two anti-PTHrP (34-53) antibodies (two lower curves) administrated at 40 µg/mice each day. Mice weight is from 30-34 g. The tumoral volume has been measured every 3 and 4 days. Accordingly, measures 1 and 2 correspond to the Tuesday and the Friday of the first week, respectively and measures 3 and 4 correspond to the Tuesday and the Friday of the second week, and so on. Accordingly, the experiment lasts about 5 weeks. Antitumoral activity of these two antibodies has also been demonstrated in vitro on human renal cancer cells 786-0 and Caki-1.

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6. The following describes the Tumor Model used in the investigation reported above. Seven-week-old male Swiss nu/nu nude mice (Iffa-Credo, St. Germain sur l'Arbresle, France) were given s.c. injections of 10 millions 786-O cells into the skin of the back. Mice weight is from 30-34 g. Tumor size was measured using calipers. Two weeks after injection, mice bearing tumors were separated each in four groups (6-8 mice each). Mice bearing tumors were injected i.p. daily with 40 µg of one of the two distinct monoclonal anti-PTHrP(34-53) antibodies (called PTH1 H413 and PTH2 E1131), with PBS or with the non relevant antibody. Tumor size was measured using calipers every 3-4 days.  $P < 0.05$  PTH1 an 2 vs. Ac Ctl and PBS.


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7. I believe the above results further demonstrate the utility of administering an anti-PTHrP antibody directed against an intermediate region of PTHrP to treat kidney cancer.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 15<sup>th</sup> day of February, 2008.

(Signature) \_\_\_\_\_

  
Thierry MASSFELDER